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Allergies: Review of the Evidence

SUMMARY

Recent changes in our perceptions of allergic IgE-mediated disease are based on evidence indicating a prominent role for both the early- and late-phase responses. The relative importance of the late-phase inflammatory reaction suggests the need for a critical re-evaluation of both diagnosis and therapy. Skin testing remains the gold standard of laboratory procedures despite new technology. Corticosteroids, acting primarily as potent anti-inflammatory agents affecting the late response, are now seen as primary therapy for allergic disease. Other drugs without anti-inflammatory properties will likely play a secondary role in future. The use of immunotherapy is also changing; this treatment may play a more prominent clinical role as a modulator of the immune response, particularly the late-phase reaction. (*Can Fam Physician* 1989; 35:1859–1862.)

RÉSUMÉ

Les récents changements dans notre perception de l'allergie médiée par les IgE sont attribuables aux constatations qui suggèrent un rôle prépondérant autant des réponses précoces que des réponses tardives. L'importance relative de la réaction inflammatoire tardive suggère le besoin d'une réévaluation critique du diagnostic et du traitement. La cutiréaction demeure l'examen par excellence des analyses de laboratoire malgré l'apparition d'une technologie nouvelle. Les corticostéroïdes, qui agissent principalement comme agents anti-inflammatoires puissants affectant la réponse tardive, sont maintenant considérés comme étant le traitement de premier choix dans l'allergie. D'autres médicaments ne possédant pas de propriétés anti-inflammatoires sont appelés à jouer un rôle secondaire dans le futur. L'utilisation de l'immunothérapie est aussi en train de changer; ce traitement peut jouer un rôle clinique plus important à titre de modulateur de la réponse immunitaire, plus précisément dans la phase tardive de la réaction.

Key words: allergic disease, immunology, immunotherapy

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ALLERGIC DISEASE affects approximately 20% of the population. Allergic disease is only one form of the many adverse reactions that have environmental causes (Table 1). An allergic reaction can be clinically distinguished from other forms of adverse reactions by the fact that they are qualitatively abnormal and are unrelated to the pharmacologic action of the offending agent.

Allergic reactions are also the result of the patient's immune response, which leads to the formation of specific antibodies or sensitized lymphocytes. Therefore, one must be able to demonstrate an immunologic mechanism to define a reaction as allergic. Most common allergic reactions are mediated by IgE antibody.

IgE Production

The IgE antibody is one of a number of immunoglobulins produced by our immune system, specifically by lymphocytes and plasma cells. Most IgE is synthesized at mucosal surfaces of the nose, lung, and gastrointestinal tract. This locally produced IgE is then transported throughout the body, and can be detected intravascularly only by sensitive radioimmunoassays, as the concentration is normally much lower than other immunoglobulins, such as IgG, IgM, or IgA.

Table 1
Classification of Adverse Reactions

Adverse reactions occurring in normal people
Overdose
Side-effects
Indirect effects (malignancy)
Agent interaction
Adverse reactions occurring in susceptible people
Disease-associated (impaired) metabolism of drugs in renal failure
Intolerance
Idiosyncratic
Allergic

Circulating IgE also binds to both basophils and tissue-bound mast cells. Therefore, IgE may be detected at mucosal surfaces or in local secretions, but also can be found within the vascular compartment, either free or bound to basophils. Tissue-bound mast cells in many organs, including the skin, nose, and lung, have IgE molecules on their surface in equilibrium with circulating antibody.

Allergic Response

Our understanding of the IgE-mediated reaction has changed as new evidence has become available (Figure 1). An allergen may interact with specific IgE bound to a tissue mast cell. This leads to a number of events within the cell, eventually resulting in the production of a wide variety of mediators, including histamine, prostaglandins, and leukotrienes.

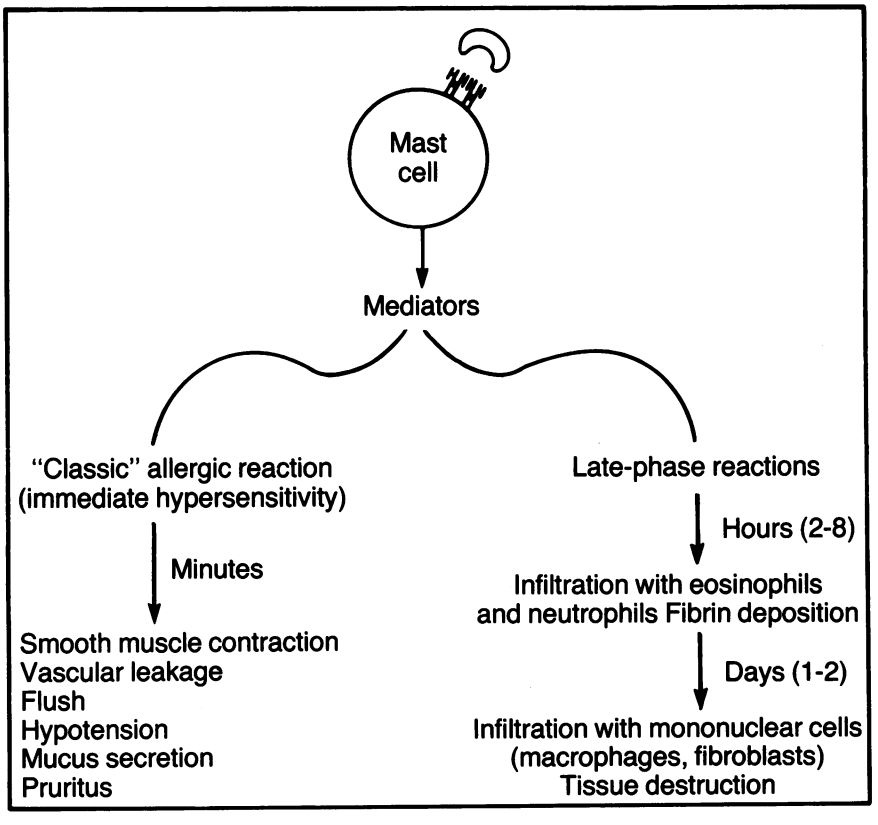
The clinical effects of mediator release are demonstrable within 15 minutes of contact between allergen and IgE. These effects include smooth muscle contraction, vascular leakage, hypotension, mucus secretion, and pruritus at the end organ. This is called the early phase and lasts only 30 to 60 minutes. During the past decade, it has become evident that there is often a secondary release of mediators beginning two hours after the initial reaction and lasting up to one to two days, called the late-phase reaction. It is marked by the presence of eosinophils, neutrophils, and mononuclear cells. This inflammatory reaction is associated with tissue destruction and can be differentiated from the early phase, in which there is no inflammatory component. The importance and significance of this late-phase reaction has evolved over the past few years, and current research suggests that this may be the more important phase of the IgE-mediated reaction.[1-3]

Clinical Syndromes

The most common clinical manifestations of IgE-mediated disease include rhinitis, asthma, urticaria, and eczema. Inhalant allergens, such as the seasonal pollens of ragweed, grasses, and trees, in addition to dust and animal allergens, are the cause of most symptoms in patients with either allergic rhinitis or asthma.

The role of food allergy in the clinical manifestations of urticaria and angioedema is less clearly defined. Double-blind oral challenges are the only accurate way of detecting food allergy for most patients. We also know that properly performed skin testing can be an effective screening mechanism. Negative results of prick tests virtually rule out the diagnosis of allergic disease, and therefore can be very helpful. A positive test result does not prove clinical relevance, but rather suggests that double-blind challenges may be indicated to determine whether the patient does have a clinical sensitivity.

Figure 1
Consequences of Mediator Release



Clinical Evaluation

The critical part of the evaluation of patients with presumed allergic disease is the clinical history. Such symptoms as nasal stuffiness, rhinorrhea, sneezing, coughing, wheezing, and shortness of breath are the most common symptoms described. It is important to define all the features of each symptom as completely as possible, in terms of the onset, severity, response to drugs, relationship to environmental stimuli, drug history, and so forth. The data must include information concerning the home environment, drugs, pets, smoking habits, and anything else that the patient thinks may be related to the symptoms.

Once an adequate history is obtained, the examination is performed. The appearance of the nasal mucosa, whether it is pale, pink, swollen, or associated with large amounts of discharge, is noted. The conjunctivae may be red and associated with excessive secretions. Otoscopic examination of the ears could reveal signs of otitis media.

A critical part of the examination is of the chest, with special attention to the presence of bronchospastic disease. Rhonchi and wheezing often are not heard in patients with mild asthma, unless forced expiration is performed. Exercise testing may also be part of the examination because it often elicits bronchospasm, despite normal results of a physical examination.

Diagnostic Tests

A number of diagnostic tests have been used in the evaluation of allergic disease.[4] Most have either proven unreliable or impractical for a variety of reasons, including cost. The three

tests most commonly used include skin testing, measurements of serum-specific IgE (with radioallergosorbent tests [RAST]), and end-organ challenge. Pulmonary function testing is an indispensible measurement for patients with asthma.

Skin testing is the cornerstone of allergy practice. It is simple and inexpensive to perform, and the results are reliable if the test is performed properly. Extensive skin testing is the most sensitive immunologic technique to determine whether an IgE reaction is occurring. Another test will only rarely detect a type I reaction when the result of a properly performed skin test is clearly negative. Epicutaneous or prick tests are the most useful, but intradermal testing can be helpful in many cases.

During the past few years, the role of measurements of serum IgE has been hotly debated. The great majority of certified allergists and clinical immunologists in North America have reached a consensus. A small but vocal minority of physicians (generally not certified allergists), however, continue to consider these tests essential to the diagnosis of allergic disease.

The role of RAST is controversial. It is generally agreed that skin testing is more sensitive than RAST. Therefore, performing RAST on patients with negative skin test results should be limited only to exceptional cases, which include patients with unreactive skin, patients receiving medications that may modify skin reactivity (antihistamines), or patients who do not co-operate well; blood-drawing may be a simpler procedure.

The role of total serum IgE assessment is limited. Elevated values do not necessarily imply allergic disease, and many patients who are clearly allergic may have normal values. This is usually not a routine test in practice.

The roles of both nasal and bronchial provocation challenges to both specific and nonspecific stimuli are now being evaluated. Nonspecific bronchial challenges seem to be of benefit in managing patients with reversible obstructive airways disease. The role of specific bronchial challenge has not been adequately assessed, and its role remains unclear. Nasal provocation has not been studied extensively in North America. Recent data have suggested that this technique is an excellent model for studying allergic disease, but a well-defined clinical role for this test has not yet been clarified.[5]

Treatment

Physicians treating patients with allergic disease use, in general, three different approaches: avoidance, pharmacotherapy, and immunotherapy.

Avoidance

The primary approach to all patients with allergic rhinitis and asthma is to avoid contact with allergens and irritants in the environment that provoke symptoms. These allergens include animals and dust; irritants include dust, smoke, pollutants, and so forth. Patients with food allergies that provoke urticaria and angioedema or eczema should avoid all offending agents.

Pharmacotherapy

If symptoms continue despite environmental control, pharmacologic treatment is generally indicated. For most patients, the primary approach has been an antihistamine administered as needed.[6] In general, antihistamines that are H_1-receptor antagonists may be helpful for many patients with allergic rhinitis. These agents bind to the end-organ receptor for histamine, and thereby compete with the histamine released from the mast cell.

Therefore, antihistamines are of optimal value when used prophylactically, before the histamine has bound to the end organ. Some of the clinical benefits of antihistamines relate to anticholinergic effects, which lead to drying of the mucosa. In the past, antihistamine efficacy was limited because of associated drowsiness, but the newer agents do not have these side-effects. Some of these agents include terfenadine, astemizole, and loratadine. Although antihistamines can be useful in the treatment of allergic rhinitis, it is important to note that nasal congestion is not affected by these drugs.

Oral decongestants may be of value for short periods, but long-term use is generally not recommended. Topical decongestants are often abused by patients on a regular basis, and this leads to rhinitis medicamentosa, a drug-induced problem potentiated by the ongoing use of topical agents. These drugs must not be used if the patient is to improve.

Sodium cromoglycate became available in the mid-1970s; this topical agent is of benefit in controlling allergic disease. Cromoglycates work by preventing degranulation of mast cells and in this way seem to affect both the early and the late phases of the allergic reaction. The side-effects associated with this drug are minimal. Unfortunately, clinical efficacy has been also somewhat limited. Sodium cromoglycate therefore has not been a particularly popular option for most patients. Cromoglycates remain an important treatment, however, and likely will become more commonly used in future.

Corticosteroids have a multitude of pharmacologic effects and are potent anti-inflammatory agents. Systemic steroids affect the late response, but do not alter the early phase.[7,8] A major therapeutic advantage of topical steroids over systemic administration may be that they not only diminish the inflammatory late response, but may also alter the early phase. The side-effects of systemic steroids are clearly much greater than those associated with topical use. Nasal topical steroids are virtually without any significant side-effects, but oral use has been associated with candidal infections of the pharynx. These are usually self-limited, and promptly disappear after the agent is discontinued.

Although both cromoglycates and topical steroids are extremely effective in the treatment of asthma, other agents, such as β_2-agonists and theophylline, have been used for years in the treatment of bronchospastic disease. These agents are bronchodilators, and act mainly by relaxing smooth muscle. These two classes of drugs do not have anti-inflammatory properties.

Recent data have demonstrated that asthma is an inflammatory disease, marked by mediators and cellular infiltrates.[1] Therefore, the primary treatment of chronic asthma should include an anti-inflammatory agent, such as cromoglycate or steroids. The role of bronchodilator drugs is less clear for patients with chronic asthma. For mild, intermittent bronchospasm, an inhaled β_2-agonist remains an important primary treatment.

Immunotherapy

The role of immunotherapy in allergic disease has been debated for many years.[9] Most investigators believe that immunotherapy acts by inducing a specific IgG antibody response to allergen. This IgG antibody can then bind to the allergen before it can interact with IgE, thereby abrogating the allergic response. Some recent evidence has suggested that immunotherapy may also alter the late response after allergic challenge of both the nose and lung.[10] This may be an important mechanism by which immunotherapy may alter the allergic response.

We do know that patients with allergic rhinitis respond well to immunotherapy for seasonal pollenosis. The data in asthma are less substantial, but there is increasing evidence that immunotherapy will alter bronchial reactivity and modulate the immune response in the bronchi.

Recent changes in immunotherapy have included the advent of modified vaccines. These vaccines have altered allergenicity, but maintain immunogenicity. They elicit an IgG-blocking antibody response, but minimize the danger of an acute allergic reaction. The only such agent currently available is a glutaraldehyde modified vaccine for both grass and ragweed. The future likely will bring a host of other modified vaccines that should demonstrate clinical efficacy with a diminished incidence of adverse reactions. The future of immunotherapy as a modulator of the immune response seems bright.

Conclusions

Our understanding of allergic disease has changed considerably during the last few years. We now understand that there is a late phase to the IgE-mediated reaction that involves a significant inflammatory component. Based on this information, allergic disease must be considered an inflammatory disease, and the approach to diagnosis and treatment should reflect these newer concepts.

From a diagnostic point of view, it has become clear that skin testing is the best technique to diagnose allergic disease. Therapeutically, anti-inflammatory agents must be considered first-line therapy in the treatment of allergic disease. Therefore, such drugs as corticosteroids and cromoglycates should be primary, rather than secondary, therapies. The role of immunotherapy has also changed over the years, and a resurgence in interest is anticipated, with the idea that one can modulate the late-phase reaction by means of allergy injections. Our concepts of allergic disease are changing rapidly, and further changes may supplant those described in this article. ■

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